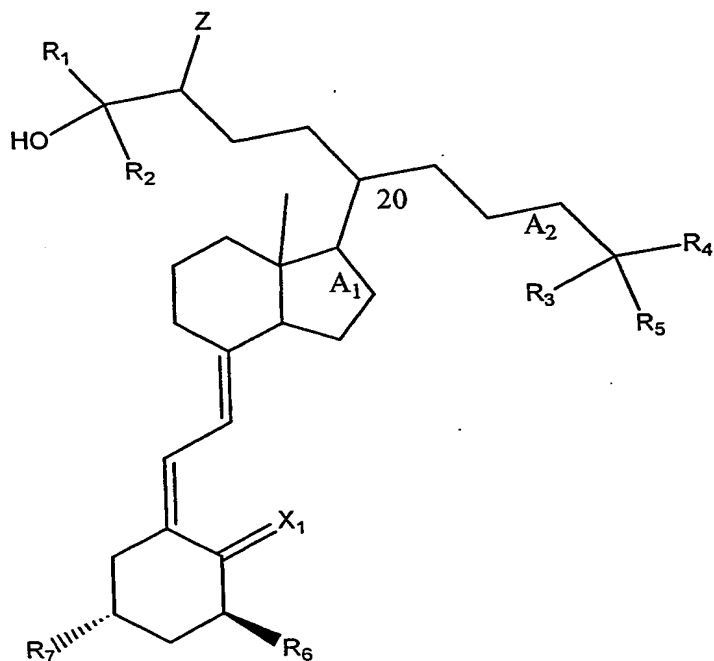


CLAIMS

1. A vitamin D₃ compound having formula I:

5



I

wherein:

A_1 is a single or double bond;

A₂ is a single, a double or a triple bond;

10 R₁, R₂, R₃ and R₄ are each independently C₁-C₄ alkyl, C₁-C₄ deuterioalkyl, hydroxyalkyl, or haloalkyl;

R₅, R₆ and R₇ are each independently hydroxyl, OC(O)C₁-C₄ alkyl, OC(O)hydroxyalkyl, or OC(O)haloalkyl;

the configuration at C₂₀ is R or S;

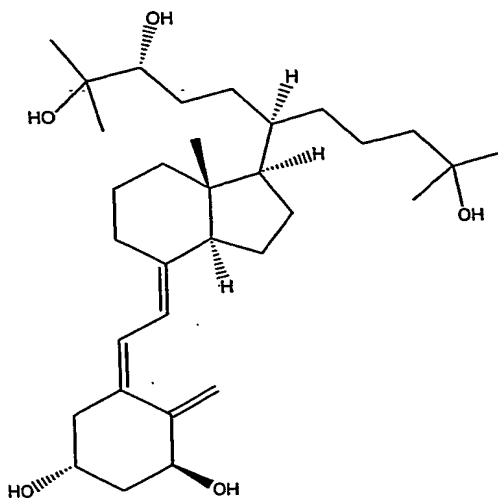
15 X_1 is H_2 or CH_2 ;

Z is hydrogen when at least one of R₁ and R₂ is C₁-C₄ deuterioalkyl and at least one of R₃ and R₄ is haloalkyl or when at least one of R₁ and R₂ is haloalkyl and at least one of R₃ and R₄ is C₁-C₄ deuterioalkyl; or Z is -OH, =O, -SH, or -NH₂; and pharmaceutically acceptable esters, salts, and prodrugs thereof.

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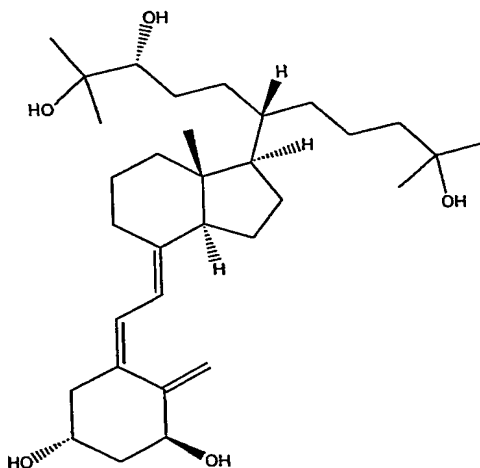
2. The compound of claim 1, wherein A₁ is a single bond.
3. The compound of claim 1, wherein A₂ is a single bond.
- 5 4. The compound of claim 1, wherein A₂ is a triple bond.
5. The compound of claim 1, wherein R₁, R₂, R₃, and R₄ are each independently methyl or ethyl.
- 10 6. The compound of claim 1, wherein R₁, R₂, R₃, and R₄ are each independently C₁-C₄ deuterioalkyl or haloalkyl.
7. The compound of claim 1, wherein R₅ is hydroxyl.
- 15 8. The compound of claim 7, wherein R₆ and R₇ are hydroxyl.
9. The compound of claim 7, wherein R₆ and R₇ are each OC(O)C₁-C₄ alkyl.
10. The compound of claim 9, wherein R₆ and R₇ are each acetyloxy.
- 20 11. The compound of claim 1, wherein X₁ is H₂.
12. The compound of claim 1, wherein X₁ is CH₂.
- 25 13. The compound of claim 1, wherein Z is hydrogen when at least one of R₁ and R₂ is C₁-C₄ deuterioalkyl and at least one of R₃ and R₄ is haloalkyl or when at least one of R₁ and R₂ is haloalkyl and at least one of R₃ and R₄ is C₁-C₄ deuterioalkyl; Z is -OH, =O, -SH, or -NH₂ when X₁ is CH₂; Z is -OH, =O, -SH, or -NH₂ when X₁ is H₂ and the configuration at C₂₀ is S; or Z is =O, -SH, or -NH₂ when X₁ is H₂ and the
30 configuration at C₂₀ is R.
14. The compound of claim 1, wherein Z is hydrogen.
15. The compound of claim 13, wherein Z is -OH.
- 35 16. The compound of claim 1, wherein Z is =O.

17. The compound of claim 1, wherein X_1 is CH_2 ; A_2 is a single bond; R_1 , R_2 , R_3 , and R_4 are each independently methyl or ethyl; and Z is $-OH$.
18. The compound of claim 1, wherein X_1 is CH_2 ; A_2 is a single bond; R_1 , R_2 , R_3 , and R_4 are each independently methyl or ethyl; and Z is $=O$.
19. The compound of claim 1, wherein X_1 is H_2 ; A_2 is a single bond; R_1 , R_2 , R_3 , and R_4 are each independently methyl or ethyl; the configuration at C_{20} is S ; and Z is $-OH$.
20. The compound of claim 1, wherein X_1 is H_2 ; A_2 is a single bond; R_1 , R_2 , R_3 , and R_4 are each independently methyl or ethyl; and Z is $=O$.
21. The compound of any of claims 17 to 20, wherein R_1 , R_2 , R_3 , and R_4 are each methyl.
22. The compound of claim 1, wherein X_1 is H_2 ; A_2 is a triple bond; R_1 and R_2 are each C_1 - C_4 deuterioalkyl; R_3 and R_4 are each haloalkyl; and Z is hydrogen.
23. The compound of claim 1, wherein X_1 is CH_2 ; A_2 is a triple bond; R_1 and R_2 are each C_1 - C_4 deuterioalkyl; R_3 and R_4 are each haloalkyl; and Z is hydrogen.
24. The compound of claim 22 or 23, wherein R_1 and R_2 are each deuteromethyl and R_3 and R_4 are each trifluoromethyl.
25. The compound of claim 21, wherein said compound is 1, 25-Dihydroxy-21-(2R,3-dihydroxy-3-methyl-butyl)-20R-cholecalciferol:



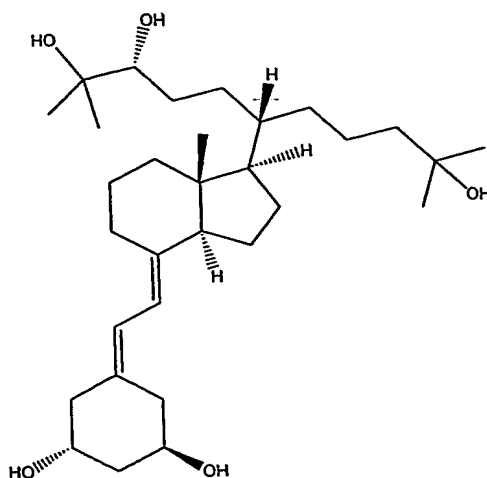
26. The compound of claim 21, wherein said compound is 1, 25-Dihydroxy-21-(2R,3-dihydroxy-3-methyl-butyl)-20S-cholecalciferol:

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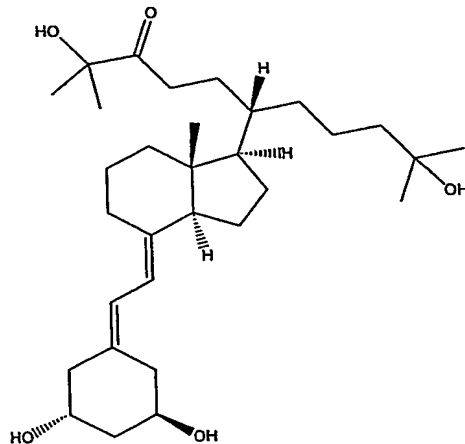


27. The compound of claim 21, wherein said compound is 1, 25-Dihydroxy-21-(2R,3-dihydroxy-3-methyl-butyl)-20S-19-nor-cholecalciferol:

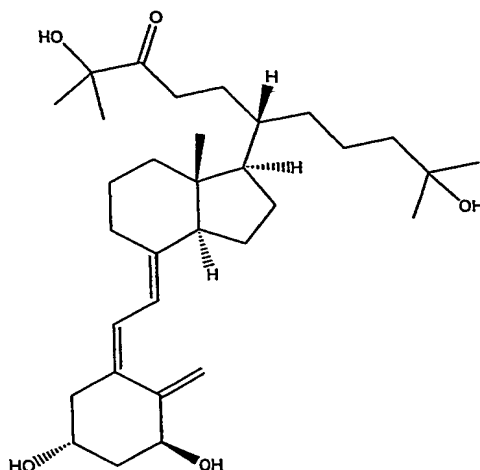
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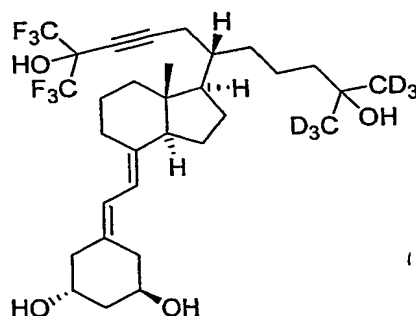
28. The compound of claim 21, wherein said compound is 1, 25-Dihydroxy-20S-21-
5 (3-hydroxy-3-methyl-butyl)-24-keto-19-nor-cholecalciferol:



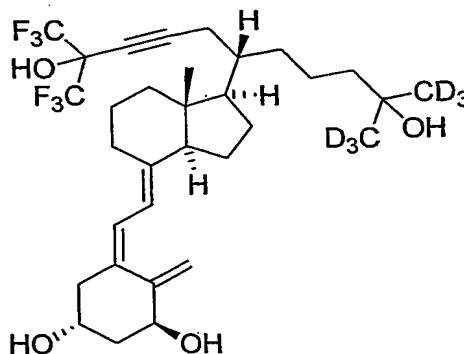
- 10 29. The compound of claim 21, wherein the compound is 1,25-Dihydroxy-20S-21-
(3-hydroxy-3-methyl-butyl)-24-keto-cholecalciferol:



30. The compound of claim 24, wherein the compound is 1,25-Dihydroxy-
21(3-hydroxy-3-trifluoromethyl-4-trifluoro-butynyl)-26,27-hexadeutero-19-nor-20S-
5 cholecalciferol:



31. The compound of claim 24, wherein the compound is 1,25-Dihydroxy-
10 21(3-hydroxy-3-trifluoromethyl-4-trifluoro-butynyl)-26,27-hexadeutero-20S-
cholecalciferol :

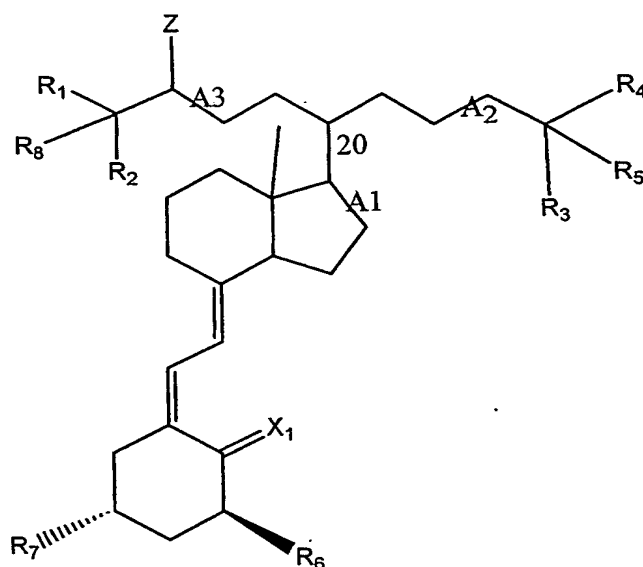


32. The compound of claim 1, wherein the haloalkyl is fluoroalkyl.
33. The compound of claim 32, wherein the fluoroalkyl is fluoromethyl or
5 trifluoromethyl.
34. A method for treating a subject for a vitamin D₃ associated state,
comprising administering to said subject an effective amount of a Gemini vitamin D₃
compound of any of claims 1 - 33, such that said subject is treated for said vitamin D₃
10 associated state.
35. The method of claim 34, wherein said vitamin D₃ associated state is a
disorder characterized by an aberrant activity of a vitamin D₃-responsive cell.
- 15 36. A method for treating a subject for a urogenital disorder, comprising
administering to said subject an effective amount of a Gemini vitamin D₃ compound of
any of claims 1-33, such that said subject is treated for said urogenital disorder.
37. The method of claim 36, wherein said disorder is bladder dysfunction.
- 20 38. The method of claim 37, wherein said bladder dysfunction is
characterized by the presence of bladder hypertrophy.
39. The method of claim 36, wherein said disorder is interstitial cystitis.
- 25 40. The method of claim 39, wherein said interstitial cystitis is characterized
by the presence of symptoms of bladder dysfunction and bladder inflammation.
41. The method of claim 36, wherein the disorder is benign prostatic
30 hyperplasia.
42. The method of claim 34, wherein said vitamin D₃ associated state is an
ILT3-associated disorder.
- 35 43. The method of claim 42, wherein said ILT3-associated disorder is an
immune disorder.

44. The method of claim 43, wherein said immune disorder is an autoimmune disorder.
- 5 45. The method of claim 44, wherein said autoimmune disorder is selected from the group consisting of type 1 insulin-dependent diabetes mellitus, adult respiratory distress syndrome, inflammatory bowel disease, dermatitis, meningitis, thrombotic thrombocytopenic purpura, Sjogren's syndrome, encephalitis, uveitis, leukocyte adhesion deficiency, rheumatoid arthritis, rheumatic fever, Reiter's syndrome, psoriatic arthritis, progressive systemic sclerosis, primary biliary cirrhosis, pemphigus, 10 pemphigoid, necrotizing vasculitis, myasthenia gravis, multiple sclerosis, lupus erythematosus, polymyositis, sarcoidosis, granulomatosis, vasculitis, pernicious anemia, CNS inflammatory disorder, antigen-antibody complex mediated diseases, autoimmune haemolytic anemia, Hashimoto's thyroiditis, Graves disease, habitual spontaneous abortions, Reynard's syndrome, glomerulonephritis, dermatomyositis, chronic active 15 hepatitis, celiac disease, autoimmune complications of AIDS, atrophic gastritis, ankylosing spondylitis and Addison's disease.
46. The method of claim 44, wherein said immune disorder is transplant rejection. 20
47. The method of claim 35, wherein said disorder comprises an aberrant activity of a hyperproliferative skin cell.
- 25 48. The method of claim 47, wherein said disorder is selected from psoriasis, basal cell carcinoma and keratosis.
49. The method of claim 35, wherein said disorder comprises an aberrant activity of an endocrine cell. 30
50. The method of claim 49, wherein said endocrine cell is a parathyroid cell and the aberrant activity is processing and/or secretion of parathyroid hormone.
51. The method of claim 35, wherein said disorder is secondary hyperparathyroidism. 35

52. The method of claim 35, wherein said disorder comprises an aberrant activity of a bone cell.
53. The method of claim 52, wherein said disorder is selected from
5 osteoporosis, osteodystrophy, senile osteoporosis, osteomalacia, rickets, osteitis fibrosa cystica, and renal osteodystrophy.
54. The method of claim 35, wherein said disorder is cirrhosis or chronic renal disease.
- 10 55. The method of claim 35, wherein the disorder is neoplastic disease.
56. The method of claim 55, wherein the disorder is selected from the group consisting of leukemia, lymphoma, melanoma, osteosarcoma, colon cancer, rectal
15 cancer, prostate cancer, bladder cancer, and malignant tumors of the lung, breast, gastrointestinal tract, urogenital tract.
57. The method of claim 56, wherein the disorder is bladder cancer.
- 20 58. The method of claim 35, wherein the disorder is neuronal loss.
59. The method of claim 58, wherein the disorder is selected from the group consisting of Alzheimer's Disease, Pick's Disease, Parkinson's Disease, Vascular Disease, Huntington's Disease, and Age-Associated Memory Impairment.
- 25 60. The method of claim 35, wherein the disorder is characterized by an aberrant activity of a vitamin D₃-responsive smooth muscle cell.
61. The method of claim 60, wherein the disorder is hyperproliferative
30 vascular disease selected from the group consisting of hypertension-induced vascular remodeling, vascular restenosis, and atherosclerosis.
62. The method of claim 60, wherein the disorder is characterized by an aberrant metabolism of a vitamin D₃-responsive smooth muscle cell.
- 35 63. The method of claim 62, wherein the disorder is arterial hypertension.

64. A method of inhibiting transplant rejection in a subject comprising administering to said subject a Gemini vitamin D₃ compound of any of claims 1-33 in an amount effective to modulate the expression of an ILT3 surface molecule, thereby inhibiting transplant rejection in said subject.
65. The method of claim 64, wherein said transplant is a solid organ transplant.
66. The method of claim 64, wherein said transplant is a pancreatic islet transplant.
67. The method of claim 64, wherein said transplant is a bone marrow transplant.
68. A method for treating a subject for hypertension, comprising administering to said subject an effective amount of a Gemini vitamin D₃ compound, such that said subject is treated for hypertension.
69. The method of claim 68, wherein the Gemini vitamin D₃ compound suppresses expression of renin, thereby treating the subject for hypertension.
70. The method of claim 68, wherein the Gemini vitamin D₃ compound is a compound having formula II:



II

wherein:

A₁ is a single or a double bond;

5 A₂ is a single, a double or a triple bond;

A₃ is a single bond, an E-double bond, a Z-double bond or a triple bond,
provided Z is absent when A₃ is a triple bond;

R₁, R₂, R₃ and R₄ are each independently C₁-C₄ alkyl, C₁-C₄ deuterioalkyl,
hydroxyalkyl, or haloalkyl; or R₁ and R₂ together with C₂₅ form a C₁-C₄ cycloalkyl or
10 cyclohaloalkyl; or R₃ and R₄ together with C₂₅ form a C₁-C₄ cycloalkyl or
cyclohaloalkyl;

R₅, R₇ and R₈ are each independently hydroxyl, OC(O)C₁-C₄ alkyl,
OC(O)hydroxyalkyl, or OC(O)haloalkyl;

R₆ is hydrogen, hydroxyl, halogen, OC(O)C₁-C₄ alkyl, OC(O)hydroxyalkyl, or
15 OC(O)haloalkyl;

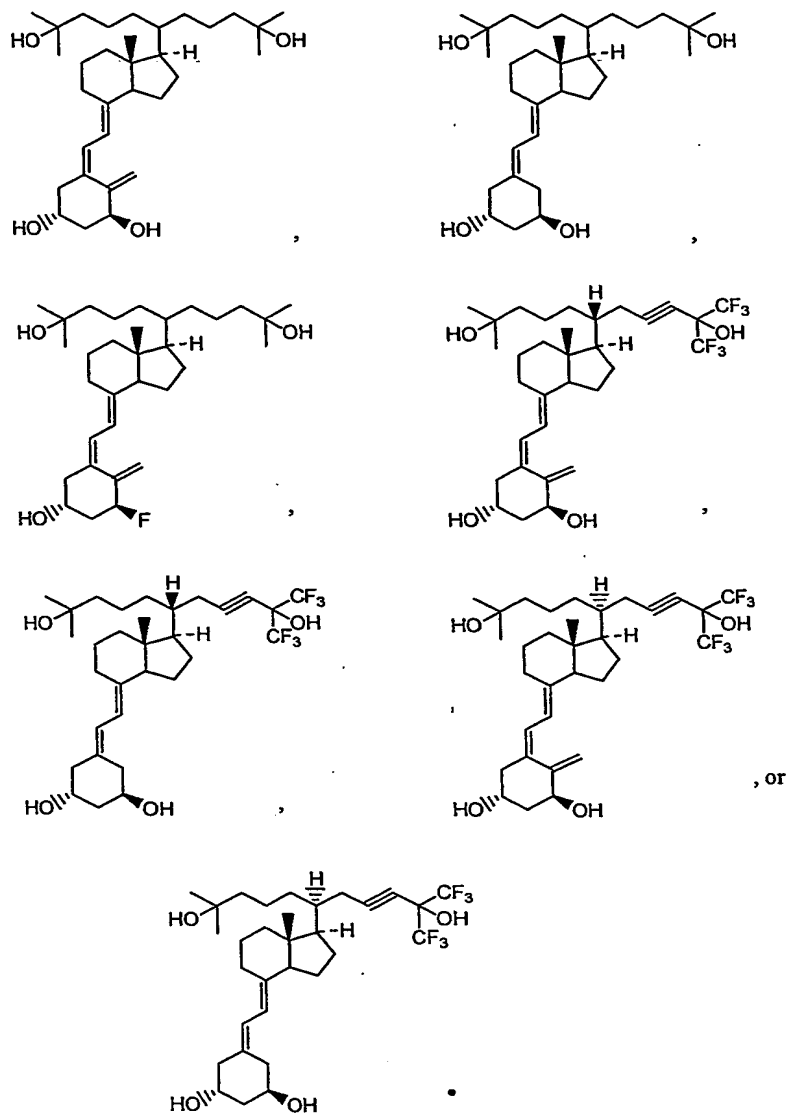
X₁ is H₂ or CH₂;

Z is hydrogen, -OH, =O, -SH, or -NH₂;

and pharmaceutically acceptable esters, salts, and prodrugs thereof.

20 71. The method of claim 70, wherein said haloalkyl, said cyclohaloalkyl and
said halogen are fluoroalkyl, cyclofluoroalkyl and fluorine, respectively.

72. The method of claim 70, wherein the compound of formula II is



73. The method of claim 70 wherein the compound of formula II is 1, 25-Dihydroxy-21-(2R,3-dihydroxy-3-methyl-butyl)-20R-cholecalciferol, 1, 25-Dihydroxy-21-(2R,3-dihydroxy-3-methyl-butyl)-20S-cholecalciferol, 1, 25-Dihydroxy-21-(2R,3-dihydroxy-3-methyl-butyl)-20S-19-nor-cholecalciferol, 1, 25-Dihydroxy-20S-21-(3-hydroxy-3-methyl-butyl)-24-keto-19-nor-cholecalciferol, 1, 25-Dihydroxy-20S-21-(3-hydroxy-3-

methyle-butyl)-24-keto-cholecalciferol, 1-Dihydroxy-21(3-hydroxy-3-trifluoromethyl-4-trifluoro-butynyl)-26,27-hexadeutero-19-nor-20S-cholecalciferol or 1,25-Dihydroxy-21(3-hydroxy-3-trifluoromethyl-4-trifluoro-butynyl)-26,27-hexadeutero-20S-cholecalciferol.

74. The method of claim 73 wherein the compound is 1, 25-Dihydroxy-21-(2R,3-dihydroxy-3-methyl-butyl)-20R-cholecalciferol, or 1, 25-Dihydroxy-21-(2R,3-dihydroxy-3-methyl-butyl)-20S-cholecalciferol.

75. The method of claim 70, further comprising obtaining the Gemini vitamin D₃ compound of formula II.

76. A method of suppressing renin expression in a subject comprising administering to a subject an effective amount of a Gemini vitamin D₃ compound such that renin expression in said subject is suppressed.

77. The method of claim 76, wherein the Gemini vitamin D₃ compound is the compound of formula II recited in claim 70.

78. A method of ameliorating a deregulation of calcium and phosphate metabolism, comprising administering to a subject a therapeutically effective amount of a vitamin D₃ compound of any of claims 1-33, so as to ameliorate the deregulation of the calcium and phosphate metabolism.

79. The method of claim 78, wherein the deregulation of the calcium and phosphate metabolism leads to osteoporosis.

80. A method of modulating the expression of an immunoglobulin-like transcript 3 (ILT3) surface molecule in a cell, comprising contacting said cell with a vitamin D₃ compound of any of claims 1-33 in an amount effective to modulate the expression of an immunoglobulin-like transcript 3 (ILT3) surface molecule in said cell.

81. The method of claim 80, wherein said cell is within a subject.

82. A method of inducing immunological tolerance in a subject, comprising administering to said subject a vitamin D₃ compound of any of claims 1-33 in an amount effective to modulate the expression of an ILT3 surface molecule, thereby inducing immunological tolerance in said subject.
- 5 83. The method of claim 82, wherein said immunological tolerance is induced in an antigen-presenting cell.
84. The method of claim 83, wherein said antigen-presenting cell is selected
10 from the group consisting of dendritic cells, monocytes, and macrophages.
85. A method for modulating immunosuppressive activity by an antigen-presenting cell, comprising contacting an antigen-presenting cell with a vitamin D₃ compound of any of claims 1-33 in an amount effective to modulate ILT3 surface
15 molecule expression, thereby modulating said immunosuppressive activity by said antigen-presenting cell.
86. The method of claim 80 wherein said cell is an antigen-presenting cell.
- 20 87. The method of claim 86, wherein said antigen-presenting cell is selected from the group consisting of dendritic cells, monocytes, and macrophages.
88. The method of any one of claims 64, 80, 82 or 85, wherein the expression of said immunoglobulin-like transcript 3 (ILT3) surface molecule is upregulated.
25
89. The method of any of claims 34-79 or 81-84, wherein said subject is a mammal.
90. The method of claim 89, wherein said subject is a human.
30
91. The method of claim any of claims 34-79 or 81-84 wherein said vitamin D₃ compound is administered in combination with a pharmaceutically acceptable carrier.
92. The method of claim 91, wherein said pharmaceutically-acceptable
35 carrier provides sustained delivery of said vitamin D₃ compound to a subject for at least four weeks after administration to the subject.

93. The method of any of claims 34-79 or 81-84, wherein said vitamin D₃ compound is administered orally.
- 5 94. The method of any of claims 34-79 or 81-84, wherein said vitamin D₃ compound is administered intravenously.
95. The method of any of claims 34-79 or 81-84, wherein said vitamin D₃ compound is administered topically
- 10 96. The method of any of claims 34-79 or 81-84, wherein said vitamin D₃ compound is administered parenterally.
97. The method of any of claims 34-79 or 81-84, wherein said vitamin D₃ compound is administered at a concentration of 0.001 µg – 100 µg/kg of body weight.
- 15 98. A pharmaceutical composition, comprising an effective amount a vitamin D₃ compound of any of claims 1-33 and a pharmaceutically acceptable carrier.
- 20 99. The pharmaceutical composition of claim 98, wherein said effective amount is effective to treat a vitamin D₃ associated state.
100. The pharmaceutical composition of claim 89, wherein said vitamin D₃ associated state is a disorder recited in any of method claims 35-79.
- 25 101. A packaged formulation comprising a pharmaceutical composition comprising a compound recited in any of claims 1-33 or 70-73, and instructions for use in the treatment of a vitamin D₃ associated state.
- 30 102. The packaged formulation of claim 101, wherein said compound is present in an amount effective to treat a vitamin D₃ associated state.
103. The packaged formulation of claim 101, wherein said vitamin D₃ associated state is a disorder recited in any of method claims 35-79.
- 35